

PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number (Optional) 616292000111	
	Application Number 10/805,804	Filed March 22, 2004	
	First Named Inventor David Charles BAULCOMBE et al.		
	1638	Examiner A. Mehta	
<p>Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.</p> <p>This request is being filed with a notice of appeal. A final rejection was mailed 29 July 2008, a Notice of Appeal was therefore due 29 October 2008. A petition for an extension of time of one (1) month until 29 November 2008 is attached hereto, along with the required fee.</p> <p>The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.</p> <p>I am the</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 60%;"> <p><input type="checkbox"/> applicant /inventor.</p> <p><input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)</p> <p><input checked="" type="checkbox"/> attorney or agent of record. Registration number 29,959</p> <p><input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____</p> </div> <div style="width: 35%; text-align: right;"> <p>_____ /Kate H. Murashige/ Signature</p> <p>_____ Kate H. Murashige Typed or printed name</p> <p>_____ (858) 720-5112 Telephone number</p> <p>_____ November 6, 2008 Date</p> </div> </div> <p>NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.</p>			
<input checked="" type="checkbox"/> Total of 1 forms are submitted.			

The three outstanding grounds for rejection of the present claims contain clear errors. The Examiner has ignored the specific requirement in all claims, that short RNA molecules (SRMs) of 20-24 nucleotides precisely are required to effect post-transcriptional gene silencing in the methods claimed.

Enclosures:

1. *Net Moneyin, Inc. v. VeriSign, Inc.*, ___ F3d ___, 2008 WL 4614511 (C.A.Fed. (Ariz.))
2. Jorgensen, R. A., *Science* (1995) 268:686-691.

The Rejection of Claims 125-130 as Anticipated by Graham (U.S. 6,537,099)

As pointed out in the Response filed 29 September 2008 (the "Response") on page 7 thereof, for anticipation, the elements of the claims must be found in a single document and be arranged and connected as described in the claim. Several cases were cited; this principle has most recently been affirmed in *Net Moneyin, Inc. v. VeriSign, Inc.*, decided by the Federal Circuit on 20 October 2008 (copy enclosed). As applicants pointed out on page 10 of this Response, in italics, *Graham never once refers to constructing vectors that will generate RNA molecules that are 20-24 nucleotides in length*. Despite alleging that Graham teaches "the produced RNA molecules can be 20-30 nucleotides in length" (see p. 7, first full paragraph of the Office action mailed 11 April 2008 and p. 3, last 4 lines of the Office action mailed 29 July 2008), the Examiner has been unable to point to any such disclosure. This is not a matter of differential interpretation, the alleged teaching just simply does not exist.

The section noted by the Examiner in column 6, lines 25-27, of Graham fails to describe production of RNA; that paragraph refers, instead, to structural gene components of a synthetic gene (and even there, limited to that derived from a viral DNA polymerase, a viral RNA polymerase, a viral coat protein or a visually detectable gene), and the size of the RNA produced by expression of such a synthetic gene is neither disclosed nor required to be of any particular size. This does not arrange the elements of present claim 125 as they are set forth in the claim and thus does not anticipate claims to methods to silence genes using vectors that produce short RNA molecules of 20-24 nucleotides.

The Rejection of Claims 116-124 as Obvious over Fire (U.S. 6,506,559) in View of Graham

Fire discloses use of RNA to effect gene silencing. In discussing the size of the operable RNA, Fire states that the duplex region of the RNA that matches the gene may have a length of at least 25, 50, 100, 200, 300 or 400 bases. Thus, Fire discloses a large genus of RNA molecules whose regions of identity apparently are expected to be quite large and vary over a wide range. While it is clear to the Examiner that Fire itself provides no motivation to silence genes using SRMs of 20-24 nucleotides, the Examiner asserts that Graham provides this motivation based on Graham's disclosure in column 6, lines 25-27, that a "synthetic gene" will have a component that comprises at least about 20-30 nucleotides. (Again, this is limited by the origins of this gene as derived from viral DNA polymerase...etc.) Focusing on this segment, the Examiner assumes that this would motivate the practitioner to construct RNA molecules for use in gene silencing that are precisely 20-24 nucleotides in length. This despite the general teaching of Graham that much longer portions of structural genes are in fact used, as exemplified, and that the overall teaching of Graham, including its examples, would motivate the reader to use much longer sequences.

Further, as pointed out on page 15 of the aforementioned Response, Graham never suggests the required length of RNA to be applied to the cells directly, as opposed to the length of a structural gene to be used in a vector. In the Advisory Action, the Examiner states that there is no reason provided for this position. No reason is needed. It is simply a fact that Graham does not disclose what length might be required for RNA supplied to the cells directly. And the Examiner himself has provided no reason to believe that the size requirements for a structural gene and for RNA administered to a cell would be the same.

Finally, the Examiner seeks to side-step, on the basis that the elected species for examination in this application is plants, applicants' argument set forth on pages 13-14, bridging paragraph, of the Response filed 29 September 2008, that since it was known that short RNA molecules would have avoided the known interferon effect induced by long dsRNA in vertebrate or mammalian systems, Fire and/or Graham would have been expected at least to have disclosed the specific and advantageous use of this size class of RNA molecules if this had been

contemplated by them. Of course, the election of plants by applicants has no bearing on the assessment of what Fire and/or Graham disclose.

The Rejection of All Claims as Obvious over Brown (U.S. 6,723,897)

Applicants refer to their arguments beginning on pages 15-17 of the aforementioned Response. In response to these arguments in the Advisory Action, the Examiner says that “clearly the length descriptions can apply to molecules used for cosuppression.”

Three points: (1) Cosuppression is not synonymous with the method of silencing by RNA interference as required by the claim. It refers to the response of plants to transgenes. (See attached Jorgensen abstract.)

(2) In the section noted by the Examiner on page 8 of the Office action mailed 11 April 2008, column 3, lines 49-67, Brown teaches only antisense expression and sense expression in the alternative, *i.e.*, using the designated sequences “**or complements thereof.**” The claims require both antisense and sense orientation expression in equal abundance.

(3) Even if Brown can be said to refer in some way to the PTGS method required by the claims (which applicants believe is stretching Brown beyond any reasonable interpretation) and that this method could include using sequences of 20 or 24 nucleotides among a wide range of other lengths, clearly Brown does not suggest the precise size range required by the claims. The range described by Brown includes sequences between 12 nucleotides and the full-length sequence. Such a wide range cannot possibly suggest the specified range set forth in the present claims.

Conclusion

The rejections outstanding are clearly in error. Graham does not meet the standard for anticipation; Fire in combination with Graham does not suggest silencing genes with short RNA molecules of 20-24 nucleotides; and Brown is completely open-ended as to any size limitations with regard to *any* method of gene suppression and, in any event, the only constructs taught by Brown only express an antisense transcript *or* a complement thereof, not both, in contrast to the requirements of the present claims.

Therefore, applicants respectfully request that all of these rejections be withdrawn and that claims 116-130 be passed to issue.

Respectfully submitted,

Dated: November 6, 2008

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